PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 307/88 // 307/87	A1	(11) International Publication Number: **WO 00/44738** (43) International Publication Date: 3 August 2000 (03.08.00)

(21) International Application Number: PCT/DK00/00032

(22) International Filing Date: 26 January 2000 (26.01.00)

(30) Priority Data:
PA 1999 00128 29 January 1999 (29.01.99) DK

(71) Applicant *(for all designated States except US)*: H. LUNDBECK A/S [DK/DK]; Ottiliavej 9, DK–2500 Valby–Copenhagen (DK).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: WEBER, Beat [CH/CH]; Wiesenstrasse 4, CH–4800 Zofingen (CH).

(74) Common Representative: H. LUNDBECK A/S; Att: John Meidahl Petersen, Ottiliavej 9, DK–2500 Valby–Copenhagen (DK).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHOD FOR THE PREPARATION OF 5–CYANOPHTHALIDE

(57) Abstract

A method for the preparation of 5–cyanophthalide in which 5–carboxyphthalide is reacted with a dehydrating agent, such as thionylchloride, and a sulphonamide, in particular sulfamide. Cyanophthalide is prepared in high yields by a convenient procedure. 5–Cyanophthalide is an intermediate used in the preparation of the antidepressant drug citalopram.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

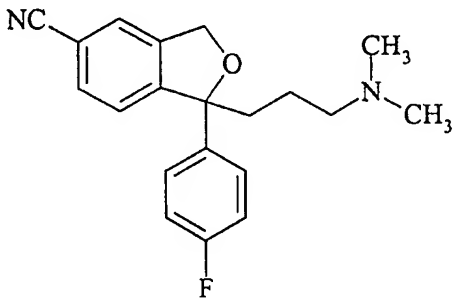
AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

METHOD FOR THE PREPARATION OF 5-CYANOPHTHALIDE

The present invention relates to a novel process for the preparation of 5-cyanophthalide which is an intermediate used for the manufacture of the well known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

Background of the Invention.

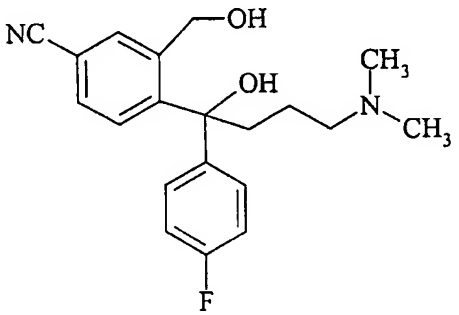
Citalopram is a well known antidepressant drug that has now been on the market for some years and has the following structure:



Formula I

It is a selective, centrally active serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982**, *6*, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, *75*, 478-486.

Citalopram may be prepared by the process described in US Patent No. 4,650,884, according to which 5-cyanophthalide is subjected to two successive Grignard reactions, *i.e.* with 4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide, respectively, and the resulting compound of the formula



Formula II

is subjected to a ring closure reaction by dehydration with strong acid.

CONFIRMATION COPY

Enantiomers of citalopram may be prepared by the method described in US Patent No. 4,943,590, i.e. by separating the enantiomers of the intermediate of Formula II and performing enantioselective ring closure in order to obtain the desired enantiomer.

Thus, 5-cyanophthalide is an important intermediate for the manufacture of citalopram and it is important to produce this material in an adequate quality, by a convenient process and in a cost-effective way.

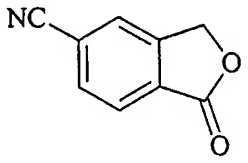
A method for the preparation of 5-cyanophthalide has previously been described in *Bull. Soc. Sci. Bretagne*, **1951**, *26*, 35 and in Levy and Stephen, *J. Chem. Soc.*, **1931**, 867. By this method, 5-aminophthalide is converted to the corresponding 5-cyanophthalide by diazotation followed by reaction with CuCN. 5-Aminophthalide was obtained from 4-aminophthalimide by a two step reduction procedure.

Synthesis of certain alkyl- and phenylnitriles from acid chlorides is described in *Tetrahedron Letters*, **1982, 23**, *14*, 1505 - 1508, and in *Tetrahedron*, **1998**, *54*, 9281.

Though a number of other methods failed, it has now been found that 5-cyanophthalide may be prepared in high yields by a convenient, cost-effective one-pot procedure from 5-carboxyphthalide.

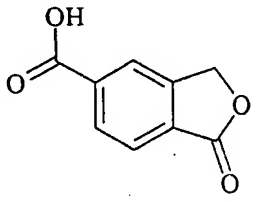
Description of the invention

Accordingly, the present invention provides a novel method for the preparation of 5-cyanophthalide



Formula IV

comprising reaction of 5-carboxyphthalide



Formula III

with a dehydrating agent and a sulfonamide of the formula $H_2N\text{-}SO_2\text{-}R$ (Formula V) wherein R is

a) NH_2, $C_{1\text{-}6}$ alkyloxy, phenyloxy,

b) phenyloxy substituted with halogen, C_{1-4}-alkyl, cyano, hydroxy, C_{1-4}-alkoxy, trifluoromethyl, nitro, amino, C_{1-4}-alkylamino or di-C_{1-4}-alkylamino, or

c) phenyl substituted with one or more electron withdrawing substituents

in order to obtain 5-cyanophthalide.

Any suitable dehydrating agent may be used and the optimal agent may easily be determined by a person skilled in the art. Examples of suitable dehydrating agents are $SOCl_2$, $POCl_3$, PCl_5, $SOBr_2$, $POBr_3$, PBr_5, SOI_2, POI_3, PI_5 and oxalylchloride. Preferably a chloro-containing agent, most preferably $SOCl_2$, is used.

The term electron withdrawing substituent is intended to mean any substituent that is sufficiently electron withdrawing to allow the reaction to proceed, such as nitro, cyano, halogen, trifluoromethyl or aminosulfonyl. 3,5-Dinitrophenyl is an example of such a phenyl group substituted with electron withdrawing substituents.

In the method of the invention, the 5-carboxyphthalide reacts with the dehydration agent in order to form the corresponding 5-haloformyl derivative which then reacts with the sulfonamide of the formula V thereby forming the 5-cyanophthalide. During the latter reaction, a catalytic amount of an acid may be necessary. The 5-haloformyl derivative may, if desired, be isolated prior to further reaction. However, preferably the reaction is carried out as a one-pot procedure without isolation of the 5-haloformyl intermediate. Preferably the reaction proceeds via the 5-chloroformylphthalide.

The sulfonamide of Formula V used in the process is preferably sulfamide, i.e. a compound of Formula V wherein R is NH_2.

The reaction is carried out neat or in a suitable solvent, such as sulfolane or acetonitrile. Preferably, sulfolane is used as the solvent.

Thus, in a preferred embodiment of the invention, 5-carboxyphthalide is reacted with sulfamide in the presence of $SOCl_2$ in a sulfolane solution

The reaction is carried out at elevated temperature. When sulfolane is used as the solvent, the reaction is preferably carried out at about 120-150 °C.

5-Cyanophthalide may be isolated in a conventional way, e.g. by addition of water, filtration and subsequent washing of the crystals. Further purification may if desired be performed by recrystallisation.

Conveniently, 1.0 to 2.0 equivalents of sulfamide and dehydrating agent, respectively, are reacted with 1.0 equivalent 5-carboxyphthalide. Preferably, 1.0 - 1.2 equivalent sulfamide is used.

By the process of the invention, 5-cyanophthalide is obtained in high yields (> about 70%). The process is much more convenient than the known process and uses more convenient and cheaper reactants and conditions. Furthermore, due to the fact that the process is a one-pot procedure the capacity is substantially increased and accordingly the costs are substantially reduced.

The 5-carboxyphthalide used as a starting material may be obtained by the methods described in US patent No. 3,607,884 or German patent No. 2630927, i.e. by reacting a concentrated solution of terephthalic acid with formaldehyde in liquid SO_3 or by electrochemical hydrogenation of trimellithic acid.

Examples

The invention is further illustrated by the following examples.

Example 1

5-Cyanophthalid

5-Carboxyphthalid (50 g, 0.28 mole) and sulfamide (31 g, 0.32 mole) were suspended in sulfolane (150 mL). Thionylchloride (41 g, 0.34 mole) was added and the temperature was raised to 130-140 °C for 2 hours. At about 90 °C, gas evolution took place. The mixture was allowed to cool to 90 °C and water (150 mL) was added. The temperature was held at 85-90 °C for 15 min and then the solution was cooled to 35 °C. The crystals were filtered off and washed with water (250 mL). The title compound was crystallised from acetic acid.Yield: 34.5 g, 77%. DSC onset: 203 °C. Purity: 98.5% (hplc, peak area). ^{1}H NMR (DMSO-d_6, 500 MHz): 5.48 (2H, s), 8.03 (2H, s), 8.22 (1H, s). ^{13}C NMR (DMSO-d_6, 125 MHz): 70.0, 116.1, 188.0, 126.0, 127.5, 129.0, 132.8, 147.7, 169.3.

Example 2

5-Cyanophthalid

Wet 5-carboxyphthalid (14 kg, approx. 6.3 kg dry, 35 mole) was suspended in sulfolane (23.5 kg). The water was removed by azeotropic distillation with toluene. Sulfamide (3.9 kg, 41 mole) and thionyl chloride (5.8 kg, 48 mole were added and the temperature was raised to

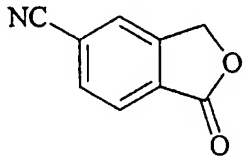
135-140 °C for 5 hours. At about 90 °C gas evolution took place. The mixture was allowed to cool to 90 °C and water (21.3 kg) was added. The temperature was held at 85-90 °C for 15 min and then the solution was cooled to 35 °C. The crystals were filtered off and washed with water (14.2 kg). The title compound was crystallised from acetic acid. Yield: 3.8 kg, 68%. Purity: 99.5% (hplc, peak area).

Example 3
5-Cyanophthalid

5-Chlorocarbonylphthalid (24.3 g, 0.124 mole) was dissolved in sulfolane (51 g). Sulfamide (13.8 g 0.144 mole) was added and the temperature was raised to 135 °C for 3 hours. At about 90 °C, gas evolution took place. The mixture was allowed to cool and water (100 g) was added. The temperature was held at 85-90 °C for 5 min and then the solution was cooled to 60 °C. The crystals were filtered off and washed with water (60 g) and acetic acid (30 g). Then the title compound was dried *in vacuo*. Yield: 19 g, 96%. Purity: 98.2% (hplc, peak area).

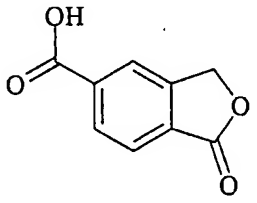
CLAIMS

1. A method for the preparation of 5-cyanophthalide



Formula IV

comprising reaction of 5-carboxyphthalide



Formula III

with a dehydrating agent and a sulfonamide of the formula $H_2N\text{-}SO_2\text{-}R$ (Formula V) wherein R is

a) NH_2, $C_{1\text{-}6}$ alkyloxy, phenyloxy,

b) phenyloxy substituted with halogen, $C_{1\text{-}4}$-alkyl, cyano, hydroxy, $C_{1\text{-}4}$-alkoxy, trifluoromethyl, nitro, amino, $C_{1\text{-}4}$-alkylamino or di-$C_{1\text{-}4}$-alkylamino, or

c) phenyl substituted with one or more electron withdrawing substituents.

2. The method of Claim 1 wherein the dehydrating agent used is $SOCl_2$, $POCl_3$, PCl_5, $SOBr_2$, $POBr_3$, PBr_5, SOI_2, POI_3, PI_5 or oxalylchloride.

3. The method of Claim 2 wherein the dehydrating agent used is $SOCl_2$, $POCl_3$ or PCl_5, preferably $SOCl_2$.

4. The method of any of Claims 1-3 wherein the sulfonamide used is a compound of Formula V wherein R is NH_2.

5. The method of any of Claims 1 - 4, wherein the reaction is carried out without isolation of the 5-haloformylphthalide intermediate.

6. The method of Claim 1 or 5 wherein the reaction is carried out neat.

7. The method of Claim 1 or 5 wherein the reaction is carried out in sulfolane or acetonitrile, preferably in sulfolane.

8. The method of Claim 5 wherein 5-carboxyphthalide is reacted with sulfamide in the presence of $SOCl_2$ in a sulfolane solution.

9. The method of any of Claims 1 - 4 wherein the 5-haloformylphthalide intermediate resulting from the reaction of 5-carboxyphthalide with dehydrating agent is isolated and then reacted with the sulfonamide.

10. The method of Claim 9 wherein the reaction is carried out in sulfolane.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00032

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/88 // C07D 307/87
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9819513 A2 (H. LUNDBECK A/S), 14 May 1998 (14.05.98), the claims; page 5, line 15 - line 25 --	1-10
A	WO 9819511 A2 (H. LUNDBECK A/S), 14 May 1998 (14.05.98), page 5, line 33 - page 6, line 5; claims 1, 20 --	1-10
A	Bull. Soc. Sci. Bretagne, Volume 26, 1951, "Phtalides substitués en 5", page 35 - page 43 --	1-10
A	Chemistry Society. London Journal., 1931, Levy et al, "Aminophthalide and Some Derivatives" page 867 - page 871 --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 May 2000	17-05-2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00032

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4650884 A (KLAUS P. BOGESO), 17 March 1987 (17.03.87) --	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/DK 00/00032

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9819513 A2	14/05/98	AU 6609898 A	29/05/98
WO 9819511 A2	14/05/98	AU 5116798 A	29/05/98
US 4650884 A	17/03/87	AT 38661 T	15/12/88
		AU 574819 B	14/07/88
		AU 4577685 A	13/02/86
		CA 1237147 A	24/05/88
		DE 3566251 A	22/12/88
		DK 89595 A	10/08/95
		DK 356285 A	07/02/86
		EP 0171943 A,B	19/02/86
		SE 0171943 T3	
		ES 545885 A	01/04/86
		FI 81338 B,C	29/06/90
		FI 852902 A	07/02/86
		GR 851894 A	03/12/85
		IE 57817 B	21/04/93
		IL 75690 A	31/10/88
		JP 1902596 C	08/02/95
		JP 6025099 B	06/04/94
		JP 61087654 A	06/05/86
		NO 853091 A	07/02/86
		NZ 212541 A	30/05/88
		PT 80913 A,B	01/09/85